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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/371,354	08/10/99	DONOVAN	S 17310

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EXAMINER	
BUNNER, B	
ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/371,354	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-18 and 28-36* is/are pending in the application.

4a) Of the above claim(s) *12,13,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11,14-18 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *7-18 and 28-36* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1,2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The preliminary amendment of 18 May 2001 (Paper No. 5) has been entered in full. Claims 1-6 and 19-27 are cancelled.

Election/Restrictions

Applicant's election with traverse of Group D, claims 7-18 and 28-36, drawn to a method for treating a cardiac muscle disorder comprising administration of botulinum toxin wherein the neurotoxin inhibits formation or release of a neurotransmitter from neurons in Paper No. 5 (18 May 2001) is acknowledged. The traversal is on the ground(s) that all the claims are directed to use of a neurotoxin to treat a cardiac muscle disorder and therefore, a single search should be sufficient to search all of the claims. This is not found persuasive because inventions A-E are different methods that require different ingredients, process steps, and endpoints. For example, Group A requires search and consideration of efficacy of therapy of neurotoxin administration to or to the vicinity of a postganglionic parasympathetic neuron, which is not required by the other inventions. Group B requires search and consideration of efficacy of neurotoxin administration to or to the vicinity of a preganglionic parasympathetic neuron, which is not required by the other inventions. Group C requires search and consideration of efficacy of therapy of neurotoxin administration to or to the vicinity of a preganglionic sympathetic neuron, which is not required by the other inventions. Group D requires search and consideration of efficacy of therapy of neurotoxin administration to a cardiac muscle, which is not required by the other inventions. Group E requires search and consideration of efficacy of therapy of administration of an anti-arrhythmic drug and botulinum toxin, which is not required by the other inventions. Further,

each of the inventions of Groups A-E encompass different subject matter and therefore, requires a unique non-coextensive search of the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-13 and 35-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5 (18 May 2001).

Claims 7-11, 14-18, and 28-34 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement filed 02 January 2001(Paper No.3) fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent/reference listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD FOR TREATING CARDIAC MUSCLE DISORDERS BY ADMINISTRATION OF BOTULINUM TOXIN A".

Claim Objections

2. Claim 8 is objected to because of the following informalities:

Claim 8 recites a non-elected species.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7-11, 14-18, and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 7-11, 14-18, and 28-34 are directed to a method for treating a cardiac muscle disorder comprising administration of the neurotoxin, botulinum toxin, to a cardiac muscle by intrapericardial injection. The neurotoxin inhibits the formation or release of the neurotransmitter, acetylcholine, from neurons in the vicinity of the cardiac muscle. The claims also recite that the cardiac muscle disorder is an arrhythmia or a bradycardia and that the amount of botulinum toxin administered is between 0.01 U/kg and 35 U/kg, between 0.1 U/kg and 30 U/kg, between 1U/kg and 25 U/kg, between 10 U and about 300 U, and between 20U and 200 U.

The specification teaches that "intrapericardial injection of BOTOX to treat an arrhythmia such as bradycardia is carried out by inserting a needle tip of a syringe through the unopened chest wall, and guided by fluoroscopy, through the thin fibrous baglike structure of the pericardium which surrounds the heart and into a pericardial sinus" (pg 31, lines 6-10). Alternative intrapericardial procedures access the normal pericardial space through the right

atrial appendage or by subxyphoid access (pg 31-32). The specification also discloses that between about 10 U and 300 U of BOTOX are administered and that the unit amount depends on the age and health of the patient, size of the patient's heart, and the mass of arrhythmic cardiac tissue of the patient's heart (pg 33, lines 4-14). However, the specification does not disclose any working examples that administer a botulinum toxin to a cardiac muscle or cells *in vitro* or *in vivo*. The specification also does not teach any specific subjects that have a cardiac muscle disorder or that are treated by any procedure with a botulinum toxin. The specification does not teach the time period in which the toxin should be administered or for how long (for example, before, during, or after surgery) and any side effects that are experienced after the administration of the botulinum toxin. The specification does not disclose a *specific* dosage of botulinum toxin that should be administered, but teaches that "botulinum toxin passes unattenuated through the lining of the gut and attacks the central nervous system...symptoms of botulinum intoxications progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles, resulting in suffocation and death" (pg 12, lines 12-16). The relevant literature reports that botulinum toxin A has only been effective in the treatment of involuntary muscle contraction disorders, dystonias, and spasticity in focal or segmental muscle regions (pg 565; Johnson, E. Annu Rev Microbiol 53: 551-575, 1999). Additionally, the primary complications of botulinum toxin therapy have been "(a) formation of antibodies and obliteration of response to type-A toxin, (b) lack of alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating ptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for repeated injection of toxin in chronic disorders" (pg 566, pp 1).

The specification teaches that arrhythmias, cardiac disorders that include bradycardia, are characterized by ventricles that "quiver in an irregular chaotic way so that little blood is pumped out of the heart and the body is deprived of oxygen" (pg 2-3, instant specification). The specification also discloses that "bradyarrhythmia or synonymously bradycardia can be defined as any disturbance of the heart's rhythm which results in a heart rate of under sixty beats per minute" (pg 7, pp 1). However, Lamanna et al. (Arch Int Pharmacodyn 293: 69-83, 1988) state that "crystalline type A botulinum toxin rapidly caused temporary bradycardia and electrocardiographic (ECG) changes in mice, rats, rabbits, and dogs" (pg 69-70, abstract). Furthermore, "the cardiac effects of botulinum are direct; they are not occurring as a response to a respiratory distress or paralysis" and "a remarkable feature of the cardiac effects of the toxin is its ready reversibility" (pg 80-81). Therefore, it is not clear why one skilled in the art would be motivated to treat an arrhythmia such as bradycardia with botulinum toxin A, if botulinum toxin A causes bradycardia.

Due to the large quantity of experimentation necessary to determine the dosage and safety of botulinum toxin, the route of administration in a subject, and the timing and duration of administration, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Johnson and Lamanna et al.), the unpredictability of the effects botulinum toxin A on a subject (see discussion and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 28-34 are indefinite because the claims do not have a step that clearly relates back to the preamble. For example, there is no step indicating how administration of a neurotoxin treats a mammalian cardiac muscle disorder.

6. Claims 31-34 are rejected as being indefinite because the administration quantity of recombinant botulinum toxin A is not clear. The numerical ranges of "about 10 U and about 300 U" and "about 20 U and about 200 U" is meaningless without the weight of the subject since the weight of the subject will determine the quantity of botulinum toxin A administered.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Schmitt et al. Bacterial toxins: Friends or foes? Emerg Infect Dis 5(2): 224-234, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Bridget E. Bunner
Art Unit 1647
June 25, 2001

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER